The Entrance into the Stem Cell Era

An Opportunity for Theraputics, Diagnostics, and Drug Discovery

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In recent years, stem cell research has emerged as one of the most exciting areas of scientific discovery and medical promise. Human embryonic stem cells capture the imagination because they are immortal and have an almost unlimited developmental potential. After many months of growth in culture dishes, these remarkable cells maintain the ability to form cells ranging from muscle to nerve to blood—potentially any cell type that makes up the human body. The proliferative and developmental potential of human embryonic stem cells promises an essentially unlimited supply of specific cell types for basic research and transplantation therapies for diseases, ranging from heart disease to Parkinson's disease to leukemia. Stem cells can also be used to study an individual's disease progression *in vitro*, opening up opportunities for personalized therapeutics and pharmaceuticals.

The early concept about how to harness stem cells was simplicity itself: harvest the unformed cells from embryos and inject them into needy recipients. The stem cells would then start rebuilding damaged hearts, pushing cancer to remission, or healing injured spinal cords. Heart disease, ALS, Parkinson's disease, and type I diabetes would all be swept away under the tidal wave of the stem cell cure. However, similar to a foreign kidney or heart transplant, injection of foreign cells would likely cause immunological rejection by the body. Destruction of human embryos for scientific research also poses numerous ethical challenges.

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In 2006, researchers in Japan lead by Dr. Shinya Yamanaka from Kyoto University had an ingenious yet simple scientific breakthrough. Their discovery, which won the Nobel Prize in Physiology or Medicine, was predicated on reprogramming mature somatic cells, such as skin fibroblasts, into embryonic-like stem cells by using viruses to add only four genes into the fibroblast's nucleus. These reprogramed cells or "induced pluripotent stem cells," iPS cells, were shown to differentiate into nearly every cell type in the body and evade the perils of rejection since the cells were the patient's own. iPS cells essentially eliminate all ethical challenges surrounding the derivation of stem cells because no embryos are destroyed.

Numerous studies since have greatly advanced our understanding of the biology that regulates stem cell differentiation and the stem cell microenvironment. However, in order to realize the clinical promise of stem cells, our fundamental knowledge of stem cell biology must be translated into suitable applications. Dr. Todd McDevitt, Associate Professor in the Wallace H. Coulter Department of Biomedical Engineering and Director of the Stem Cell Engineering Center, argues that the nascent field of stem cell engineering will be increasingly necessary to realize the scientific community's envisioned goals of stem cell based therapeutics, diagnostics and drug discovery platforms.

Engineering conditions for iPS cells to differentiate homogeneously into a specific cell type is currently difficult. One study demonstrated that although global gene expression of iPS cells looks amazingly similar to embryonic stem cells, there are distinct regions in the genetic code of iPS cells that do not get reprogrammed properly. In those regions, iPS cells' genomes still resembled the tissues from which they came from, suggesting that the cells had not been fully set back to the embryonic stage. Consequently, iPS cell cultures can become contaminated with other cell types, which do not have the same coveted therapeutic potential.

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Manually sorting these stem cells is time consuming and difficult; using chemical approaches can damage the DNA inside. To address the problem, post-doctoral fellow Dr. Ankur Singh and Dr. McDevitt, in collaboration with Professor Andres Garcia have demonstrated a tunable process that separates cells according to the degree to which they adhere to a substrate inside a tiny microfluidic device.

The adhesion properties of the human iPS cells differ significantly from those of the cells with which they are mixed, allowing the potentially-therapeutic cells to be separated to as much as 99 percent purity. The high-throughput separation process, which takes less than 10 minutes to perform, does not rely on labeling technologies such as antibodies. Because it allows separation of intact cell colonies, it avoids damaging the cells, allowing a cell survival rate greater than 80 percent. The resulting cells retain normal transcriptional profiles and differentiation potential. Using inexpensive, disposable "cassettes," the microfluidic system could be scaled up to filter increased volumes of cells and to allow the feasible possibility of commercialization and manufacture of stem cell therapies for humans.

The Georgia Tech researchers applied their new understanding of the adhesive properties of human iPS cells to develop a quick, efficient method for isolating these medically important cells. Their work, published in the journal *Nature Methods* [1], represents an innovative conversion of basic stem cell biology, biomaterials, and engineering into a strategy with therapeutic potential. During testing, iPS cell cultures were first allowed to attach to the microfluidic device before being subjected to the flow of buffer fluid. Cells with a lower adhesive strength detached from the substrate at lower flow rates. By varying the flow rate, the researchers were able to separate specific types of cells with high purity from mixtures in which those cells accounted for only a few percent of the total.

Since their discovery, iPS cells have captured the imagination of researchers and clinicians seeking to develop patient-specific therapies. Reprogramming adult tissues to embryonic-like states has countless prospective applications in regenerative medicine, drug development, and basic research on stem cells and developmental processes. To this point, more than 2100 research papers on iPS cells have been published since 2006, indicating a highly active and rapidly developing research field. Purification of iPS cells marks a significant achievement in realizing the promise of stem cells for therapies and scientific advancement. While much remains to be learned and significant challenges remain in iPS cell research, the development of reprogramming techniques represents a breakthrough that will ultimately open many new avenues of research and therapy.

References

[1] Singh, Ankur *et al.* (2013). Adhesion strength–based, label-free isolation of human pluripotent stem cells, *Nature Methods*, 10, 438–444.